Surgical and biochemical outcomes of phosphaturic mesenchymal tumors causing tumor-induced osteomalacia in the head and neck region

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Abstract

Objectives: We aimed to report the surgical outcomes of phosphaturic mesenchymal tumors causing tumor-induced osteomalacia in the head and neck. Design: A retrospective cohort study Setting: A tertiary care academic hospital Methods: This study analyzed nine patients who underwent surgical excision of phosphaturic mesenchymal tumors in the head and neck region. The primary sites were two in the maxilla and ethmoid sinus, and one in the intracranial, skull, parotid gland, maxillary sinus, and nasal cavity in each patient. Outcomes were compared with those in the extremities and trunk (n = 32). Results: Five of nine patients (56%) developed residual disease/local recurrence associated with low serum phosphate level after initial surgical excision. At the last follow-up, the biochemical parameters were normalized in four of the five patients after re-excision without any medication. The local recurrence/residual disease risk was significantly higher for the head and neck compared with the extremities and trunk (56% vs. 25%, p = 0.048). The rate of remission (normalized serum phosphate without medication) at final follow-up was similar in both groups after re-excision (head and neck vs. extremities and trunk, 86% vs. 73%, p = 0.827). Conclusions: Phosphaturic mesenchymal tumor resection in the head and neck region was challenging because of its complex anatomy and proximity to the brain or other crucial organs, which was associated with high local recurrence/residual disease rate. However, biological remission was achieved in the majority of the patients after re-excision.

Original article

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Key points:

There have been a few reports on the surgical outcomes of phosphaturic mesenchymal tumors causing tumor-induced osteomalacia in the head and neck.

Tumor-induced osteomalacia is a rare and underreported condition because treating clinicians are unaware of its clinical characteristics. We highlighted our experience with Tumor-induced osteomalacia cases in the head and neck regions.

Phosphaturic mesenchymal tumor resection in the head and neck region was associated with high local recurrence/residual disease rate.

Before definitive resection, surgeons should discuss with their patients the difficulty of obtaining clear margins due to the complex anatomy.

Re-excision lead to biological remission in the majority of the patients after re-excision.

1 Introduction

Tumor-induced osteomalacia (TIO) is a rare paraneoplastic disorder caused by tumors that secrete fibroblast growth factor 23 (FGF23).[1] Because of its role in renal phosphate handling and vitamin D synthesis, TIO is associated with decreased renal phosphate tubular reabsorption, hypophosphatemia, and low active vitamin D levels. Patients are often affected by the muscular vulnerability and bone pain for a prolonged time before diagnosis due to osteomalacia.[2,3]

The majority of tumors that cause TIO are classified as phosphaturic mesenchymal tumors (PMTs).[4] Head and neck regions were the second most constant localization of tumor (26%), next to the lower limbs (46%).[2] Previous research on PMT in the head and neck region was primarily case reports with short-term follow-ups.[5-7] Although comprehending the long-term surgical result and the cases with residual/local recurrent tumors is crucial for clinical administration, only a few reports have focused on nonremission and recurrent PMT cases.[8] There remains a paucity of studies on long-term surgical and biochemical outcomes of PMT in the head and neck area.

Therefore, the purpose of this study was to determine the long-term surgical and biochemical outcomes of PMT in the head and neck region, particularly in nonremission and recurrent cases. These outcomes were also compared with PMT in the extremities and trunk.

2 Patients and Methods

We followed the STROBE reporting guidelines. Between 1998 and 2022, 67 patients with TIO were identified in our hospital's database. Among them, nine patients with PMT in the head and neck regions who underwent surgical excision were involved in this research. In comparison, 32 patients with PMT in the extremities and trunk who had surgical excision were analyzed. Regarding the remaining 26 patients, tumors were not detected by imaging studies in 18, the histology and clinical courses were consistent with malignant tumors

in 3, and only examinations were conducted at our hospital in 5. These 41 patients' clinical records and imaging studies were reviewed retrospectively.

Most patients suspected of having TIO were referred to the corresponding department (oral and maxillofacial, orthopaedic, otolaryngology, neurosurgery, etc.) from the endocrinology department. Multiple examinations were carried out to identify the primary tumor, including FGF23 venous sampling, 18-fluorodeoxyglucose positron emission tomography with computed tomography (FDG-PET/CT), ^{99m}Tc bone scintigraphy, somatostatin receptor scintigraphy, or magnetic resonance imaging (MRI).[9]The diagnosis and localization were made following a review of the histopathology and radiology results with a multidisciplinary discussion. Serum phosphate, alkaline phosphatase (ALP), and bone-specific alkaline phosphate levels were measured regularly for postoperative monitoring. All the patients were asked to visit the endocrinology department for follow-up at 2–3 months postoperatively and every 3–6 months thereafter. Endocrinologists continued medical treatments for patients whose serum phosphate levels did not return to normal after surgery. Biochemical remission was defined as normalized serum phosphate and serum ALP levels without any medication. Pathology findings were consistent with PMT, showing the proliferation of bland spindle to stellate cells that were immunohistochemically positive for FGF23.

FGF23 values were measured by an FGF-23 ELISA Kit, which exclusively detects biologically active intact FGF23. FGF23 levels [?]30 pg/ml under hypophosphatemic condition clearly differentiate FGF23-related hypophosphatemia from hypophosphatemia due to other causes.[10,11] Immunohistochemistry for FGF23 was conducted with monoclonal FGF23 antibody.

All patients underwent surgical excision of the tumor with the aim of achieving R0 or R1 margin.[12] Extended curettage was used in patients with bone tumors at the extremity or trunk who were expected to have functional impairment after surgery: the tumor was removed with a curette, and the margin was expanded with high-speed burring.[13]

Case reports for cases 4[14] and 5[15]in Table 1 are available elsewhere. The detailed results of these multimodal tests for cases 2, 8, and 9 were reported in our group's previous article (cases 2, 8, and 9 in the current study are equivalent to cases 4, 1, and 27 in ref. 9).

Chi-square tests were used to compare the categorical variables between the groups. Two-tailed probability (P) value of <0.05 was considered to be statistically significant. To conduct statistical analyses, R version 4.2.1 was used.

All procedures were carried out in accordance with the Declaration of Helsinki's ethical standards and were approved by our institutional ethical board [Ref. P2017016 and 2879]. All the patients provided written informed consent.

3 Results

3.1 Patient demographics, imaging, and biochemical work-up

The patient details were included in Table 1. There were six male and three female patients. The median age at diagnosis was 53 years (interquartile range [IQR], 41–63 years), the median follow-up after initial resection was 64 months (IQR, 20–98 months), and the median maximum tumor size was 20 mm (IQR, 11–36 mm).

The patient's symptoms on presentation to a doctor were bone or joint pain in multiple locations. The time elapsed between the initial patient's complaints and the diagnosis of TIO ranged from 5 to 126 months with a median delay of 72 months. Only 22% of patients were correctly diagnosed within 2 years, while 56% were correctly diagnosed between 5 and 10 years after the onset of symptoms. X-rays revealed pseudofractures in all of the patients (Fig. 1a–e). Whole-body ^{99m}Tc bone scintigraphy demonstrated increased uptake in multiple bones, including ribs, vertebrae, and femur, in four available cases. The endocrine work-up revealed the following laboratory findings: low serum phosphate (median 1.3 [IQR, 1.2–1.7] mg/dL, normal range, 2.7–4.6 mg/dL), high serum ALP (median 281 [IQR, 251–355] U/L, normal range, 38–113 U/L), normal to low serum corrected calcium (median 8.7 [IQR, 8.5–9.0] mg/dL, normal range, 8.8–10.1 mg/dL), and normal

to high intact parathyroid hormone (median 64 [IQR, 43–123] pg/mL, normal range, 15–65 pg/mL). The serum FGF23 was elevated (median 241 [IQR, 194–3750] pg/mL). The clinical signs, imaging studies, low serum phosphate levels, and elevated serum FGF23 levels all pointed TIO.

To determine the localization of the primary tumor, systemic venous sampling of FGF23 was performed in five patients. FGF23 levels were highest in the internal jugular vein in two patients, the external jugular vein, subclavian vein, and superior vena cava in one patient each (Table 1). In all patients, MRI revealed a tumor in the head and neck region. Somatostatin receptor scintigraphy was performed, which enabled tumor visualization in all four available patients. FDG-PET/CT revealed mild uptake (SUV max median 5.7, IQR 5.1–6.2) in the suspected tumor.

3.2 Surgical and biochemical outcomes

Of the nine patients, four (44%) underwent a biopsy before definitive surgery, which confirmed the PMT diagnosis. Patients underwent surgical excision of the tumor with R0 (n = 1) or R1 margin (n = 8). There was no surgical complication. Residual/local recurrent tumors with low serum phosphate were seen in five patients (56%) after initial surgical resection, including four residual and one local recurrent tumor. Of these, four patients (80%) underwent tumor re-excision, and serum phosphate and FGF23 levels were normalized without any medication at the final follow-up. Residual/local recurrent tumors were detected at median 19 months (range, 9–80 moths) form initial resection by imaging studies. At the time of the last follow-up, eight patients (89%) were still alive, while one died from an acute myocardial infarction. The four patients (44%) were continuously recurrent tumor-free after the initial surgery. Only one patient (11%) was living with a recurrent tumor after surgical excision and taking oral phosphate and activated vitamin D.

3.3 Comparison with outcomes of PMT in the extremity and trunk

The patient details were shown in Table 2. The rate of residual disease/local recurrence with low serum phosphate was significantly higher in cases at the head and neck (56%) compared with cases at the extremities and trunk (25%, 8 of 32, p = 0.048). Re-excision was performed in 25% of patients (2 of 8) with extremity or trunk tumors which is lower compared with that in the patients with head and neck tumors (80%, 4 of 5). At the last follow-up, the rate of biochemical remission without medication was similar in both groups (89% of the patients with head and neck tumors and 75% of patients with extremity and trunk tumors, p = 0.827). At the last follow-up, medical treatment was continued in one patient (11%, 1 of 9) with a head and neck tumor and eight (25%, 8 of 32) with extremity and trunk tumors.

3.4 Case presentation

Case 1 in Table 1:

Here, we present a representative patient with a residual tumor. A 38-year-old male was referred to the evaluation of worsening pain in his knee, hips, and lower back without an injury history. The medical history of the patient was unremarkable. On laboratory results, low serum phosphate (1.3 mg/dL), high ALP (524 U/L), intact parathyroid hormone (117 pg/mL), and FGF23 (660 pg/ml) levels were observed. Functional imaging with somatostatin receptor scintigraphy showed increased uptake in the nasal region (Fig. 2a). A contrast-enhanced maxillofacial area CT revealed a mass in the nasal cavity (Fig. 2b and c). An incisional biopsy was performed, and microscopic examination revealed a vascular-rich tumor composed of FGF23-positive bland spindle cells (Fig. 2d). A PMT diagnosis was made. Two weeks after the initial biopsy, endoscopic resection of the tumor was performed. However, low serum phosphate and high FGF23 levels persisted, and MRI revealed a residual tumor at the left cribriform plate one year after resection (Fig. 2e and f). After the patient underwent re-excision under the endoscopic endonasal technique, the serum phosphate levels returned to normal. The last follow-up was negative for tumor recurrence or residual tumor.

4 Discussion

We have reported the surgical and biochemical outcomes for head and neck TIO. PMT resection in the head

and neck region was associated with high local recurrence/residual disease rate (56%), which was significantly higher than that of the extremities and trunk (25%). However, biochemical remission was achieved in the majority of the patients after re-excision at the last follow-up (89%, 8 out of 9).

Most of the previous reports concerning the head and neck TIO were small case series often mixed with other sites, which had short-term follow-ups within two years after surgical excision.[5-7,16,17] Pal et al. reported surgical excision in 30 cases TIO in various sites, which resulted in remission in 73% of the patients, whereas disease persistence and tumor recurrence in 18% and 9% of the cases, respectively.[18] Zhu et al. analyzed 43 patients with sinonasal tumors, including PMT, odontogenic fibroma, and hemangiofibroma, which were associated with TIO.[19] In the series, a high local recurrence rate or nonremission was found (12%). The other report illustrated the seven patients with TIO in the paranasal sinus, intracranial, and maxilla who underwent surgical excision.[20] They demonstrated that four of seven (57%) had persistent illness after surgical removal, and three patients were managed by external beam radiation treatment for recurrent tumors. Consistent with these reports, our data demonstrated a great residual disease/local recurrence rate in the head and neck PMT. However, in most of our patients, biochemical remission was attained after re-excision without radiation treatment. We believe that re-excision of the residual/local recurrent tumor without radiation therapy is a practical treatment option. In contrast to our findings, Li et al. reported that the refractory rate was the lowest in head and neck tumors (7.5%) compared to other sites.[8] However, they did not state the details of localization of the tumor, surgical methods, and complications after surgery for the head and neck tumors. In our residual/recurrent cases, craniotomy was conducted due to the proximity of the brain in three cases. The surgical process, surgical margin, and localization of the tumor presumably contributed to the differences in outcomes.

Complete surgical excision with wide margins was the cornerstone of PMT management.[21,22] The main surgical challenge of resection of head and neck PMT is the difficulty of obtaining a clear margin because of the anatomical complexity and proximity of the brain or other important organs. Previous studies showed that soft tissue PMT with an irregular boundary observed on imaging tended to infiltrate into subcutaneous fat.[21] Furthermore, bone PMT demonstrated invasion into cancellous and cortical bone.[22] These findings suggest that in patients with these imaging features, resection of infiltrative margin in soft tissue tumor or resection of thinned cortical bone may be required to reduce the risk of local recurrence/residual disease. However, excessive removal of the surrounding tissues may increase the risk of surgical morbidity, particularly in cases of head and neck PMT. Surgeons need to balance the risk of surgical morbidity and local recurrence/residual disease.

TIO is a rare and underreported condition because treating clinicians are unaware of its characteristic, clinical, and biochemical profiles.[3] Through this research, we highlighted our experience with TIO cases including the head and neck regions. A significant time gap between the initial presentation until the diagnosis existed even in the presence of severe symptoms in our series. Other challenges included the difficulty of distinguishing PMT from other incidental findings on imaging studies. Especially in the head and neck area, apical periodontitis was encountered, which was suspected to be a tumor that caused TIO (Fig. 3a–f). Furthermore, X-linked hypophosphatemic rickets/osteomalacia is one of the possible differential diagnoses in patients with osteomalacia who have abnormal findings in the alveolar bone area, which can lead to a variety of dental complications, including apical periodontitis.[23] These findings will raise awareness and provide valuable insights into the treatment of issues associated with this rare disease in the head and neck region.

We would like to acknowledge the limitations of our study. First, this study involving a heterogeneous and small group of patients. Second, our study is a retrospective review and there are selection, indication, and expertise biases concerning both the initial surgery and subsequent procedures. Third, patients were treated over two decades, and we were unable to adjust for important confounders, including evolution in treatment strategies and medical/surgical/imaging management/techniques. A histopathology and radiology review at an institutional multidisciplinary board meeting, we believe, has reduced these biases.

In conclusion, PMT in the head and neck area demonstrated a high local recurrence/residual disease rate.

However, biochemical remission was achieved in most patients at the last follow-up. Before definitive resection, surgeons should discuss with their patients the difficulty of obtaining clear margins due to the complex anatomy of the region and the proximity of important organs.

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Figure legends

Figure 1.

An 87-year-old man with a phosphaturic mesenchymal tumor in the ethmoid sinus (case 9). **a)** Radiograph of the right knee demonstrates coarse trabecular bone involving distal femur, proximal tibia, and proximal fibula with the presence of pseudofractures.**b)** Radiograph of the left humerus demonstrates pseudofractures.**c)** A lumbar spine radiograph reveals diffuse osteopenia with variable decreases in vertebral body heights. **d)** ^{99m}Tc bone scintigraphy reveals increased tracer uptake in multiple ribs, vertebral bodies, the left humerus, the right distal femur, the right proximal tibia, and the left distal tibia, indicating multiple pseudofractures. **e)** Coronal brain MRI reveals a lobulated mass (white arrow) in the ethmoid sinus with extension to the skull base.

Figure 2.

A 38-year-old man underwent excision of a nasal cavity PMT (case 1).**a)** Somatostatin receptor scintigraphy reveals increased uptake in the tumor region (white arrow). The tumor (white arrow) is visible in the nasal cavity on preoperative **b)** axial and **c)**coronal CT images. **d)** Pathological examination reveals a vascular-rich tumor composed of bland spindle cells that were immunohistochemically positive for FGF23 (inset). T1-weighted contrast-enhanced MRI of the nasal cavity **e)** axial and**f)** coronal views show a recurrent tumor (white arrow head).

Figure 3.

A 60-year-old man underwent excision of a left mandibular lesion suspected of being a tumor that caused TIO. Histological findings showed dense immunocompetent cell infiltration, which was consistent with apical periodontitis. A radiolucent area (white arrow) is visible on orthopantomography **a)** and periapical radiographs **b)** at the mandibular #5 teeth area. Preoperative CT images **c)** axial and **d)** sagittal show bone destruction in the mandibular region (white arrow). **e)** An enhanced mass on preoperative T1-weighted contrast-enhanced MRI (white arrow). **f)** FDG-PET/CT presents increased uptake in the mandibular area (white arrow).

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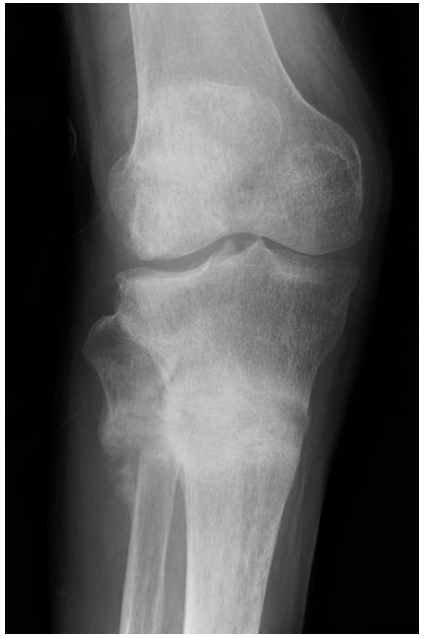
Figure 1

a



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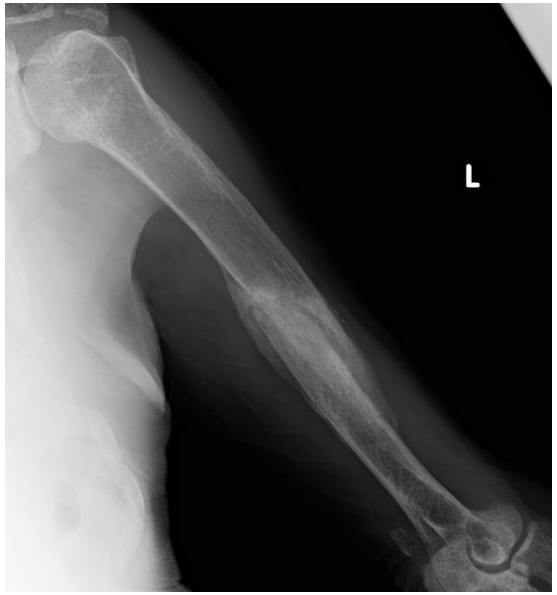

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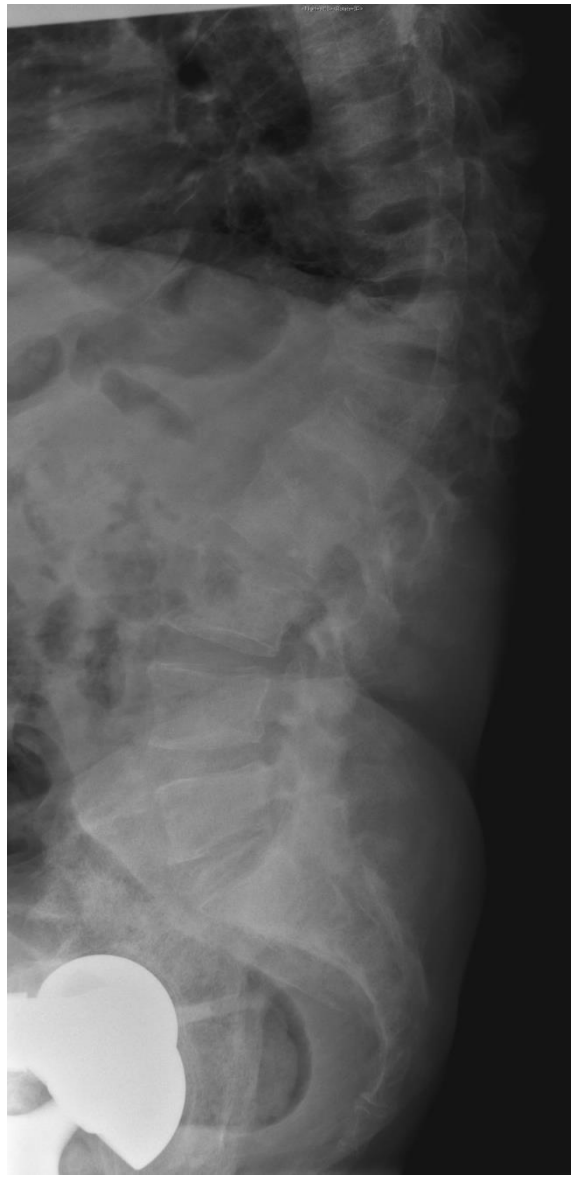

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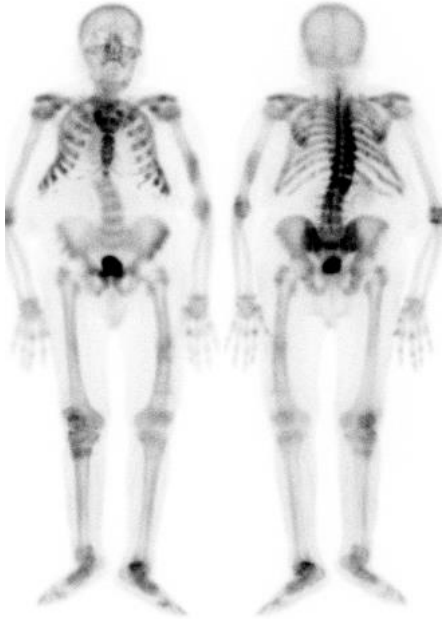

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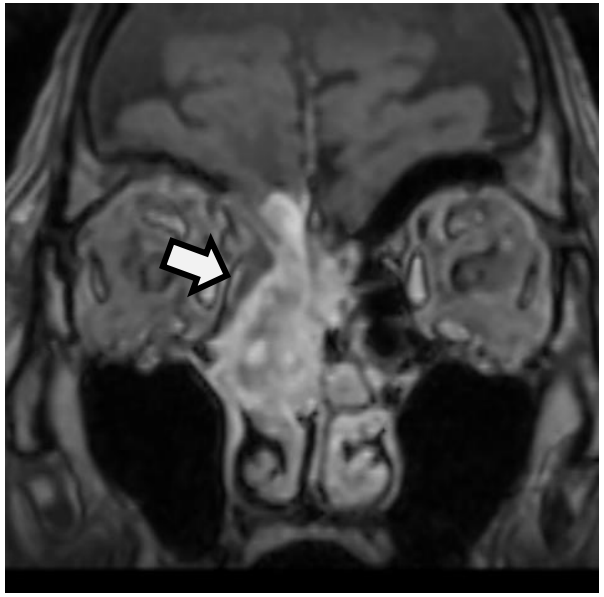

Figure 2

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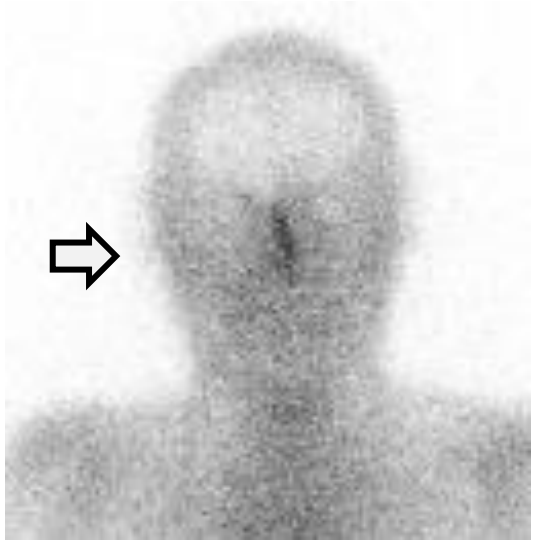

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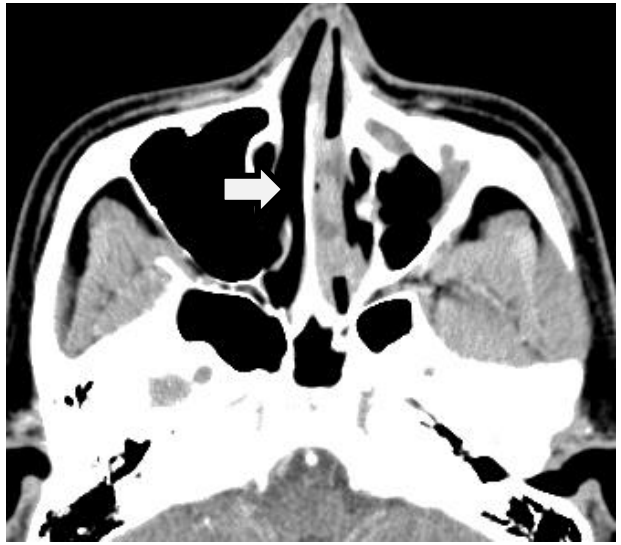

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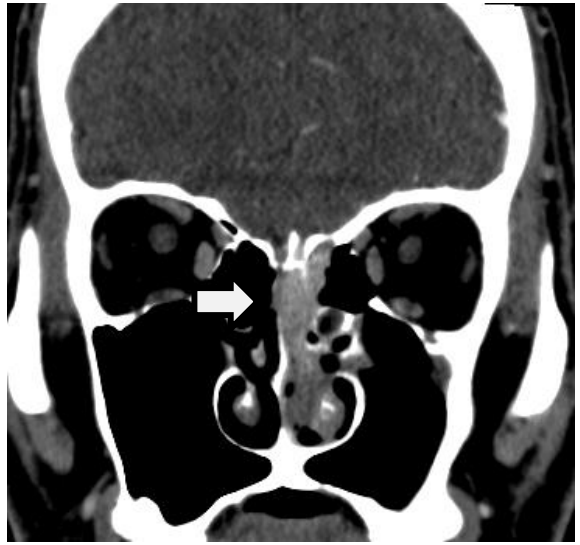

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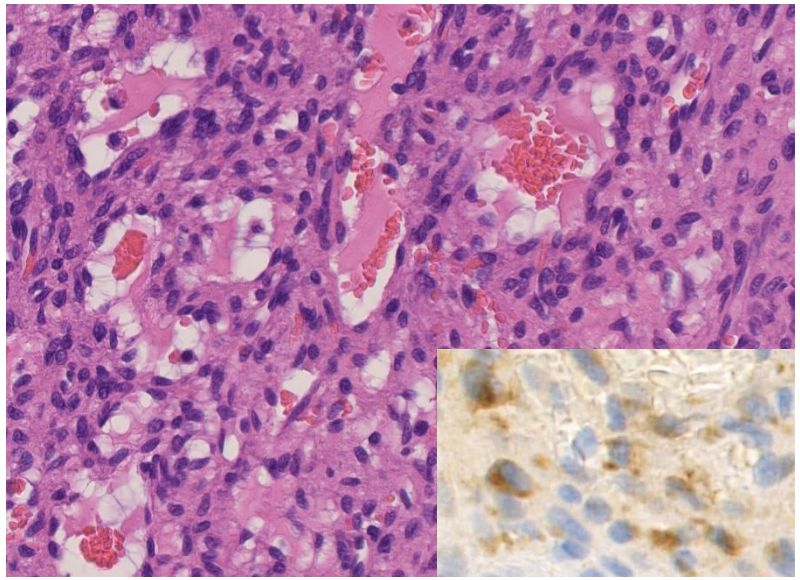

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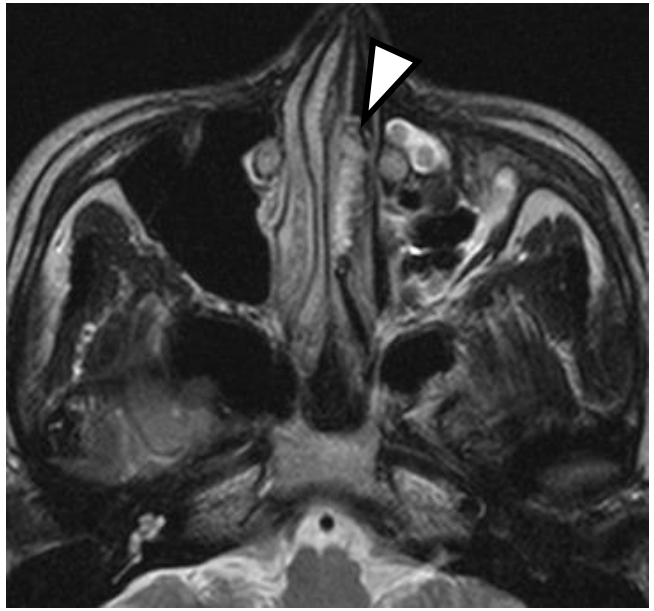

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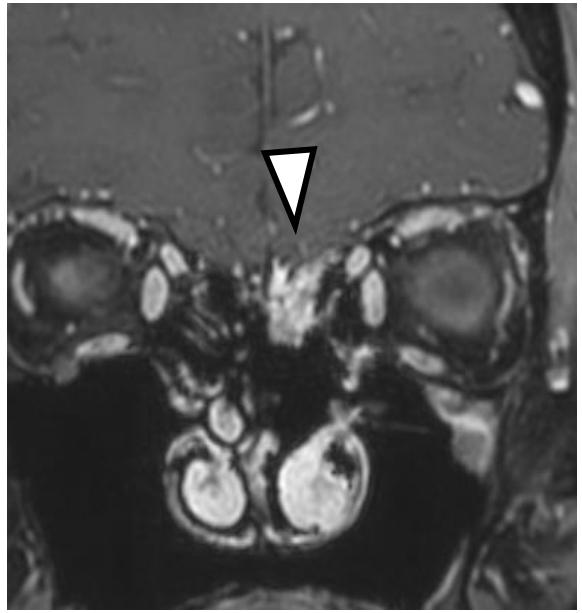

Figure 3

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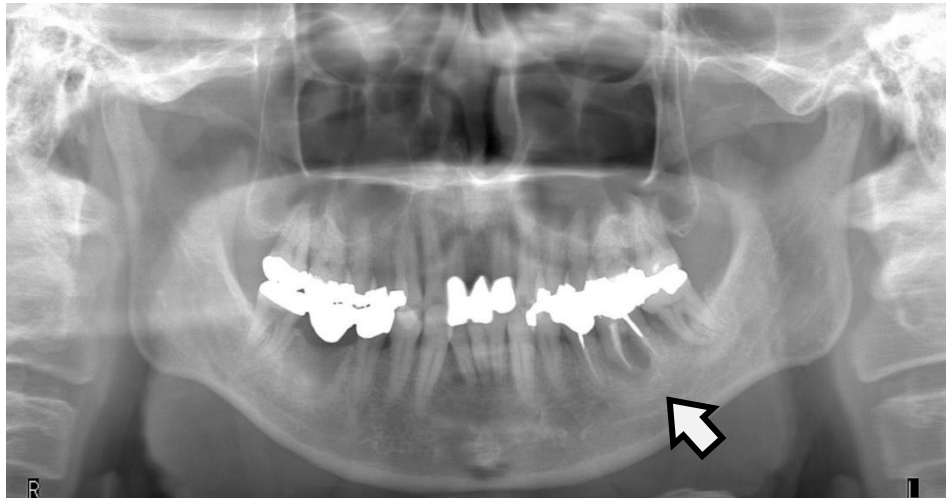

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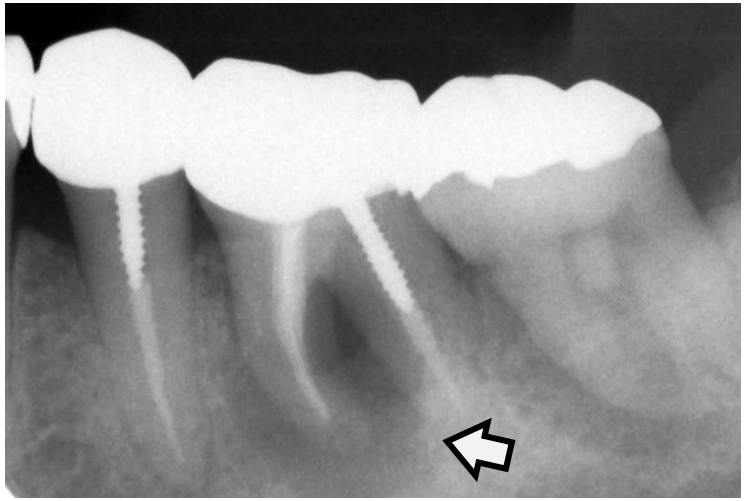

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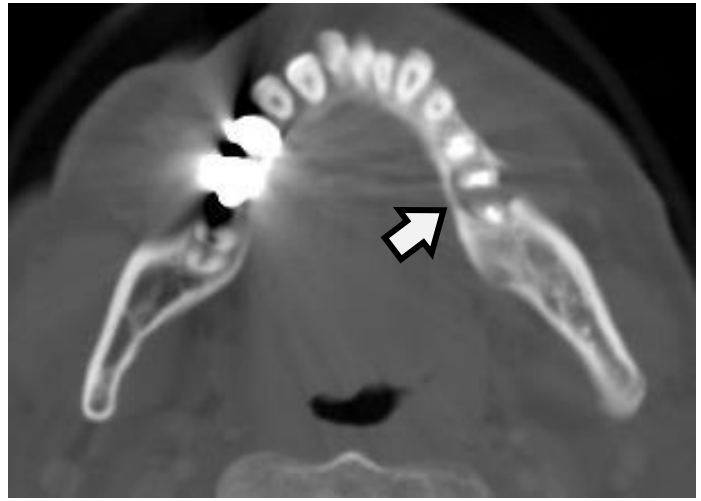

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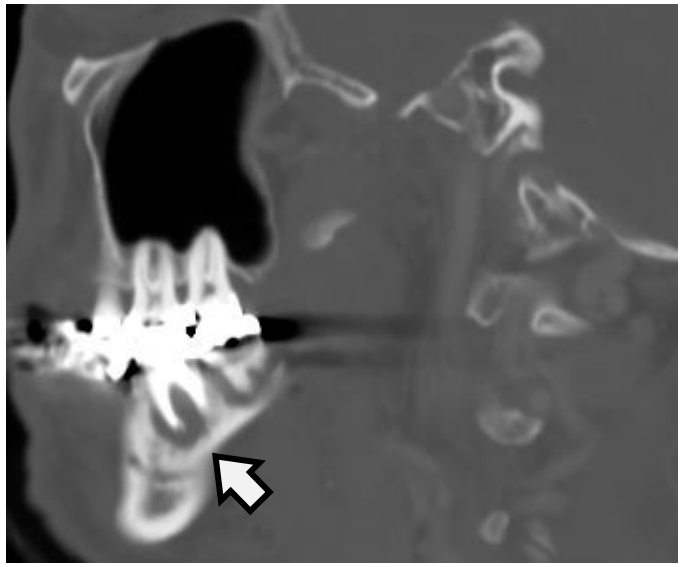

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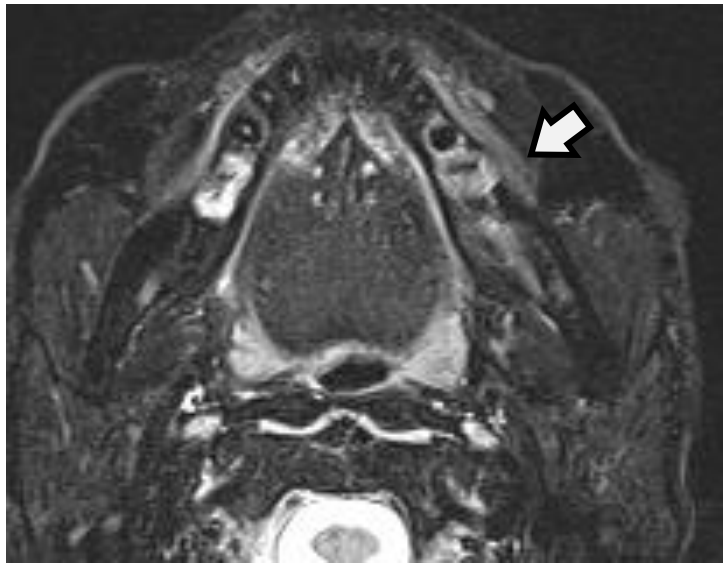

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